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Systematic or Meta-analysis Studies

# Evolution of treatment strategies for oligometastatic NSCLC patients – A systematic review of the literature

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ABSTRACT

*Background:* The concept of oligometastatic disease (OMD) has expanded the scope of potentially curative therapy for metastatic NSCLC. However, large uncertainties remain regarding its definition and optimal management strategies. We therefore conducted a systematic review to investigate the value of various multimodality treatment concepts.

*Methods:* We searched the available literature in Pubmed, Medline and EMBASE using the terms "oligomet*", "synchron*", "oligorec*", "metachr*" "NSCLC", "lung cancer" and "stage IV" and included studies reporting treatment regimens and outcomes on radically treated patients with either "synchronous", "metachronous" or "mixed" OMD. Only de-novo diagnosis of OMD was considered. The impact of patient and treatment characteristics on overall survival (OS) and time trends in patterns of care were investigated.

*Results:* 54 studies published between 1987 and 2018 were included. Despite a wide range of OMD definitions, 90.1% of patients were treated for a single metastasis. Systemic therapy was used as backbone treatment for most patients. Although surgery was the preferred local treatment in earlier studies, the use of stereotactic radiotherapy increased rapidly after 2011. No OS difference was observed between surgery or radiotherapy as the treatment of primary tumor or metastases, respectively. A time trend towards improved OS after 2011 could be detected.

*Conclusions:* While evidence in favor of radical treatment is emerging, most studies remain retrospective and mainly evaluate patients with singular metastases. While surgery, stereotactic radiotherapy and chemotherapy are the cornerstones of current treatment strategies, future clinical trials need to address the high risk of distant metastases by integrating targeted or immunotherapy.

## Introduction

Metastatic NSCLC has long been thought of as incurable and treatment consisted mainly of palliative chemotherapy (CHT). Local treatments, such as surgery or radiotherapy, with palliative, non-ablative doses were restricted to symptom control. The concept of oligometastatic disease (OMD) is currently challenging this dogma by defining an intermediate stage of metastatic disease with a more favorable disease biology and dynamic. OMD is characterized by a limited number of metastatic lesions and a low overall metastatic burden that opens a therapeutic window for radical treatment to all cancer sites, the locoregional primary tumor and oligometastases. Originally coined by Hellman and Weichselbaum in 1995 [34,17], the idea has gained interest particularly during recent years through several developments: (a) improved diagnostics for early and more accurate detection of low disease burden, (b) clinical implementation of minimally invasive and high-precision locally-ablative treatments (LAT) such as video- or robotic assisted surgery (VATS, RATS) or stereotactic (body) radiotherapy (S(B)RT), (c) more effective systemic treatments that have lead to a prolonged overall survival (OS) of metastatic patients and (d) a better biological and clinical understanding of tumor biology.

In the treatment of oligometastatic NSCLC, early efforts have mainly focused on the radical treatment of readily resectable lesions, like brain and adrenal metastases [5,33,43,37]. With the improvement in diagnostic imaging and novel developments in non-invasive LAT modalities such as SBRT, more reports have surfaced recently that investigate radical treatment of all disease sites, potentially leading to improved clinical outcome [13,14,19].

5-year OS as high as 86% has been reported for oligometastatic NSCLC patients using a curative approach [24]. This is in contrast to < 10% 5-year OS in stage IV NSCLC patients treated with palliative intent [20]. However, a major problem is the difficulty to reliably

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predict which patients may benefit most from a radical treatment approach and to exclude patients at high risk for rapid progression to a polymetastatic state. First steps have been undertaken to define OMD on a biological level, but a thorough understanding is still lacking and even this limited strategy has not seen widespread introduction into routine clinical practice [25].

A standardized definition of OMD in terms of the number of metastases and affected organs does also not exist to date. In addition, there is widespread confusion about different terms used in the field. Although no formal consensus on the definitions exists, it is currently widely accepted to consider OMD for up to five separate lesions in up to three different organs which are potentially amenable for LAT [42,2,29].

For the reasons described above, patient collectives in the available literature are heterogenous. Thus, 5-year OS of radically treated patients varies widely and ranges between 8% and 80% [2]. Nonetheless, the oligometastatic state has been recognized clinically as a distinct entity in NSCLC [2] and was recently included in the 8th version of the TNM-classification of NSCLC and in the ESMO and NCCN guidelines with recommendations for LAT [15,31,11].

Robust, large-scale prospective data for oligometastatic NSCLC is lacking, although important prospective trials on oligometastases have been reported with potentially practice-changing results, as a significant impact on OS could be demonstrated [28,13,14,19].

In summary, despite the inclusion of OMD into practice guidelines and the wide adoption of this concept in clinical practice for treatment of NSCLC, the level of evidence is still low. Our goal was to conduct a systematic search of the literature to investigate the role of intensified multimodality treatment for synchronous and metachronous OMD and elucidate patterns of inclusion criteria, multidisciplinary treatment strategies and clinical outcomes. As the concept of OMD is evolving, we focused this systematic review on synchronous and metachronous oligometastases only, and excluded oligoprogression and -persistence as distinct clinical scenarios.

## Materials and methods

Data collection and analysis was conducted according to the PRISMA statement (http://www.prisma-statement.org/). We searched the available literature in Pubmed, Medline and EMBASE between 1985 and October of 2018 using the terms “oligomet*”, “synchron*”, “oligorec*”, “metachr*” “NSCLC”, “lung cancer” and “stage IV”.

*Publications were included if the following criteria were met:*

1. Histologic confirmation of NSCLC
2. Stage IV disease with either synchronous metastases (metastasis diagnosed ≤3 months after primary tumor) or (b) metachronous metastases (metastasis diagnosed > 3 months after primary tumor)
3. Oligometastatic state (≤8 metastases); Lymph node metastases to the mediastinum were considered local-regional disease.
4. Radical treatment intent for all disease sites in ≥85% of patients. Treatments considered radical were surgical excision or radiation doses ≥50 Gy EQD2 (in case of radiotherapy as the only treatment to the respective disease site), but not systemic treatment alone, e.g. chemotherapy or tyrosine kinase inhibitor (TKI) administration.
5. ≥8 patients included in the respective study

*Exclusion criteria were:*

1. Reviews/meta-analyses, case reports and book chapters
2. Reports based on national tumor registries/outcome reports (e.g. SEER, NCDB) to avoid multiple inclusion of patients
3. Multiple primary cancers
4. ≥9 metastases
5. Studies with less than eight patients analyzed
6. Reports published before 1985
7. Reports including small cell lung cancer (SCLC) patients
8. Studies reporting about a patient cohort that was previously included in another study
9. Local recurrence and oligorecurrence not sufficiently discriminated from the above-mentioned definition of OMD.

The following data was extracted: number of patients; age of patients; median and 5-year OS; histology; metastasis number; location and time of oligometastases occurrence; type of treatment to primary tumor and all metastases.

Reporting of outcomes was structured as follows: patients were classified as “synchronous” if diagnosed with distant metastasis within 90 days of primary tumor diagnosis or if the study design or the outcomes implied this. Remaining patients were defined as “metachronous”. For studies that contained both syn- and metachronous metastases, patients were classified accordingly, if outcome data was reported separately for both collectives. In that case, both collectives were counted as separate studies in the analysis where reported data differed (e.g. median OS). If no separate outcome was described, publications were defined as “mixed”. Metastatic sites were classified according to the TNM staging system.

### *Literature search*

The initial search yielded 1165 studies of which 1102 were excluded based on non-matching abstracts and titles. Subsequently, we identified matching references in the remaining 63 studies and repeated this process iteratively until no new, matching studies could be identified. This process lead to 394 publications that were assessed in detail for eligibility. After excluding another 340 studies based on our inclusion criteria, a total of 54 studies were used for further analysis (Fig. 1). 29 of those were reporting synchronous tumors and three focused on metachronous disease. 15 studies included both, synchronous and metachronous tumors but only reported combined outcomes and were thus classified as “mixed”. Seven publications reported outcomes for metachronous and synchronous tumors separately and patients were assigned to the respective collective. For quantitative analysis these patient groups were counted as individual studies where feasible (amounting to a grand total of 61 studies). Literature search and data extraction were performed independently by two investigators.

### *Statistical considerations*

Assumption of normality was tested using the Shapiro-Wilk method. For non-normally distributed data, the Kruskal-Wallis Rank Sum test was used to determine differences between groups. Statistical analysis was performed using R version 3.5.2 with packages dplyr, survival, Hmisc and ggplot2 in the most current versions as of October 2018.

## Results

A total of 54 studies were used for further analysis after literature search and application of inclusion criteria (Table S1). Seven reports presented distinct data for both, synchronous and metachronous patients and were therefore analyzed separately. Publication frequency differed markedly with 1.2 and 4 publications per year before and after the median publication year 2011, respectively. Six reports (11%) were prospective studies, accounting for 142 (7.1%) out of 1994 analyzed patients. Studies included 32.7 patients on average (range: 10–181 patients). Most studies included < 40 patients so that the 14 largest publications accounted for more than 50% of the total number of analyzed patients.

### *Patient- and tumor characteristics*

Median age at the time of oligometastases diagnosis was 61 years.

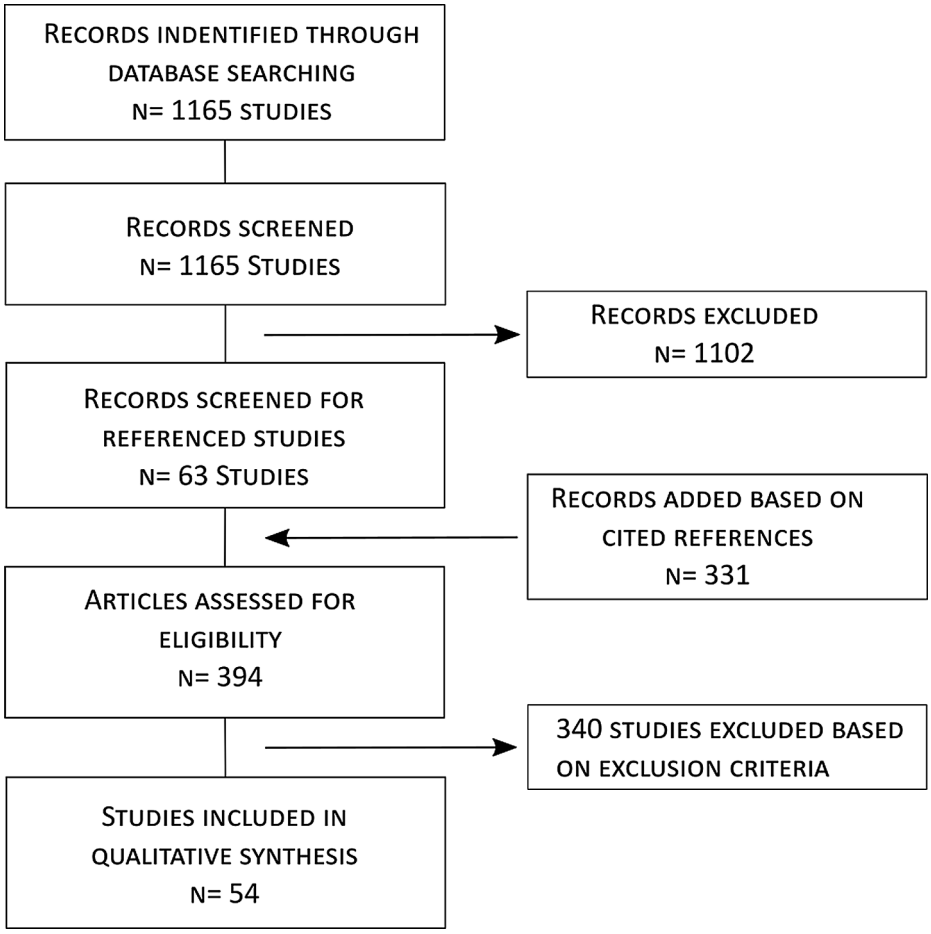


**Fig. 1.** Flow diagram of literature search strategy.

60% of patients were diagnosed with adenocarcinoma, 23% with squamous cell carcinoma and 17% with other histologies (Table 1). On the level of individual metastases, 55% were located in the brain, 17% in the lung, 11% in the adrenal gland and 17% in other organs (Fig. 2C). When assessing the number of metastases, 90.5% of patients had one, 7.1% two, 1.6% three and < 1% four or five metastases, respectively (Fig. 2D). Few studies reported individual patients with an undetermined number of small metastases in the brain, amounting to < 0.5% of included patients.

59% of publications did not apply any formal definition of oligometastases and the remainder used an upper limit of metastases between one and eight as criterion (Fig. 2A). In 9% of reports the definition of OMD applied more or modified criteria (e.g. lymph node status, number of metastases after induction CHT) and were classified as "other". When analyzing the inclusion criteria in each study, we found a discrepancy between the pre-specified inclusion criteria and the actually treated number of metastases per included patient: 41%, 17%, and 17% of publications effectively treated a maximum of one, two and three metastases per patient, respectively (Fig. 2B). 15% of included records did not provide the effective number of included metastases and only 4% treated patients with five metastases radically.

Of the studies labeled "metachronous" or "mixed" (n = 25), 20% defined metachronous OMD as metastases arising more than three months after the primary diagnosis;. 16% used two or more months; one study defined four months as the threshold; 8% five or six months, respectively; and one study defined it as more than two years after primary diagnosis. 40% of publications did not offer any concise definition. In the case of metachronous OMD, studies included patients with a median DFI of 14.3 months using an LAT-only approach, although their definition allowed for a DFI as short as three months after initial tumor diagnosis.

*Management of OMD*

*LAT to primary tumor*

In the majority of patients (76%), the local treatment modality for the primary tumor was surgical resection (Fig. 3; Table 1). Neoadjuvant or adjuvant radiotherapy was combined with surgery in 9% of patients. Primary definitive radiotherapy was used in 22%, delivered as conventional RT (with or without concurrent chemotherapy) or SBRT.

*LAT to metastases*

Distant metastases were treated by surgery in 65% of cases (Table 1). Surgical interventions were followed by adjuvant radiation in 27% of patients; this was a frequent approach especially with stereotactic radiotherapy (SRT) of cerebral resection cavities. Radiation as primary treatment modality was more common for treatment of metastases than for primary tumors (69% vs. 35%). In 10 studies, metastases were exclusively treated with ablative SRT (three of those prospective). Other treatments such as thermoablation were reported in < 1% of cases.

*Systemic therapies*

In synchronous OMD studies, systemic treatment was used in a variety of settings: The most common application was in an adjuvant/maintenance setting (performed in 54% of studies, in 2 studies combined with RT), followed by neoadjuvant application (29.7% of studies, in 3 studies combined with RT). TKI-treatment was allowed in only 18.9% of studies, in 48.6% the systemic treatment remained unspecified and in 37.8% of OMD studies, no systemic treatment was

**Table 1**
Comparison of patient and treatment characteristics of studies including patients with synchronous, metachronous or mixed metastases.

| *All Studies* | | *Value* | *Range (over studies)* | *Number of eligible studies* |
|---|---|---|---|---|
| *Year Published* | Median | 2011 | 1987–2018 | 61 |
| *Number of metastases (% of all metastases)* | 1 metastasis | 90.5% | 11–100 | 46 |
| | 2 metastases | 7.1% | 2–52 | 23 |
| | 3 metastases | 1.6% | 1–26 | 12 |
| | 4 metastases | 0.7% | 0–18 | 6 |
| | 5 metastases | 0.1% | 0–4 | 3 |
| *Median overall survival* | Median | 19.6 months | 6.2–52.9 | 46 |
| | Mean | 22.3 months | ± 11.2 (SD) | |
| | Weighted Mean By # of pts. per study | 24 months | | |
| *1-year overall survival* | Median | 66.5% | 25–100 | |
| | Mean | 66.3% | ± 18.3 (SD) | |
| *5-year overall survival* | Median | 21% | 0–86 | |
| | Mean | 27% | ± 18.7 (SD) | |
| *Histology* | Adeno | 60.4% | 14–90 | 50 |
| | Squamous | 22.7% | 0–55 | 51 |
| | Other | 17% | 0–93 | 48 |
| *Metastatic sites (percentage of total metastasis count)* | ADR | 10.8% | | 49 |
| | BRA | 54.1% | | 49 |
| | HEP | 1.9% | | 49 |
| | LYM | 2.7% | | 49 |
| | OSS | 8.3% | | 49 |
| | OTH | 3.5% | | 49 |
| | PLE | 0.3% | | 49 |
| | PUL | 18.4% | | 49 |
| *Primary tumor local treatment (percent of patients)* | Adjuvant RCT | 0.6% | | 51 |
| | Adjuvant RT | 6.8% | | 47 |
| | Definitive conv. RT | 5.3% | | 50 |
| | Definitive RCT | 10.2% | | 50 |
| | Neoadjuvant conv. RT | 0.1% | | 50 |
| | Neoadjuvant RCT | 1.6% | | 52 |
| | SBRT | 6.1% | | 48 |
| | Surgery | 75.6% | | 59 |
| | Unspecified/other RT | 4.7% | | 51 |
| *Distant tumor local treatment (percent of patients)* | Adjuvant RT | 26.7% | | 51 |
| | Primary conv. RT | 4.7% | | 55 |
| | Stereotactic RT | 30.1% | | 56 |
| | Surgery | 64.8% | | 58 |
| | Thermoablation | 0.1% | | 58 |
| | Unspecified/other RT | 7.8% | | 57 |
| *Systemic treatment (percent of patients)* | Adjuvant/ maintenance CHT | 21.3% | | 46 |
| | Neoadjuvant CHT | 6.2% | | 51 |
| | None | 32.5% | | 47 |
| | Targeted Therapy | 5.3% | | 49 |
| | Unspecified/other | 31% | | 49 |

applied in the OMD setting. For metachronous OMD, most studies allowed for application of systemic therapy after LAT (60%) while the minority reported on neoadjuvant (30%) and simultaneous treatment (20%). Overall, in synchronous studies 75.0% of patients received chemotherapy in contrast to 61.2% in metachronous and 54.4% in mixed studies. 5% of cases received targeted therapy as a part of the multidisciplinary approach, in most cases agents targeting the EGF or VEGF pathway. No publications in our analysis reported the use of immunotherapy, i.e. agents targeting CTLA-4 or the PD-1/PD-L1 pathway. Only two studies completely waived systemic treatments for all included patients [18,22].

### *Time trend analysis*

Over time, patient assignment to LAT shifted towards a wider utilization of radiotherapy for primary tumors with a shift from 23% to 41% of patients in studies published before and after 2011. There was also a change towards wider adoption of stereotactic RT instead of conventionally-fractionated RT with an increase from 0% to 23% for primary tumors and from 15% to 60% for distant metastases of irradiated patients. This reflects the broader adoption of stereotactic RT in clinical practice and particularly its application for oligometastatic disease within the radiation oncology community (Fig. 4). Finally, the number of patients receiving no systemic therapies decreased from from 45% to 24% using the same cutoff publication year.

### *Overall survival*

Median OS was reported in 53 studies and was 22.3 months ( ± 11.2 months SD) on average, excluding seven studies where the median was not reached (Table 1). When adjusted for patient number, this changed to a mean of 24.1 months. Median OS differed significantly between studies published before and after 2011 (the median publication year) with 16.1 months and 27.1 months, respectively (Fig. 4). Median 1-year OS among all studies was 66% and median 5-year OS reached 21%.

Upon comparison of survival between synchronous, metachronous and mixed collectives, mean median OS was about 20 months and mean 5-year OS about 25%, respectively (Fig. 5, Tables S2–S4). There was no statistically significant difference between above-mentioned collectives regarding median OS (P = 0.54) and 5-year OS (P = 0.84). Virtually all studies reported application of systemic therapy, either neoadjuvant (30%), simultaneous (20%) or adjuvant (55%). Therefore, the effect on OS could not be investigated.

To analyze a potential association between OS and type of LAT to either primary tumor or distant metastases, percentage of patients per study that were treated with surgery (as opposed to other modalities i.e. SBRT, radio-chemotherapy, conventionally-fractionated RT, etc.) was entered into a linear regression model weighted by number of patients in the respective study. To avoid bias from worse OS in older studies, only publications that were published starting from 2011 (the median publication year) were included in this model. Type of LAT for primary tumor (P = 0.65, Fig. 6A) or metastases (P = 0.73, Fig. 6B) had no statistically significant effect on median OS.

## Discussion

Over the past years the phenomenon of OMD has gained significant attention and has resulted in an increasing number of publications. But despite some recently published, prospective randomized trials [13,14,19], the role as well as the optimal clinical implementation of LAT to the primary tumor and metastases remains to be elucidated. Existing systematic reviews of the available published data on this subject focus on the verification of the oligometastatic state as a clinical entity [2], analyze distinct clinical scenarios [39,30], or review only part of the available literature [1]. This study aimed to perform an updated systematic review of the entire literature on radical multidisciplinary treatment of oligometastatic NSCLC to evaluate different strategies regarding local and systemic treatment. To our knowledge, this is the first analysis to systematically summarize the literature on radical multidisciplinary treatment of oligometastatic NSCLC, specifically investigating time trends in the management of OMD and their influence on OS.

The majority of studies included in this review did not formally specify OMD. This is partly due to their publication date before the term

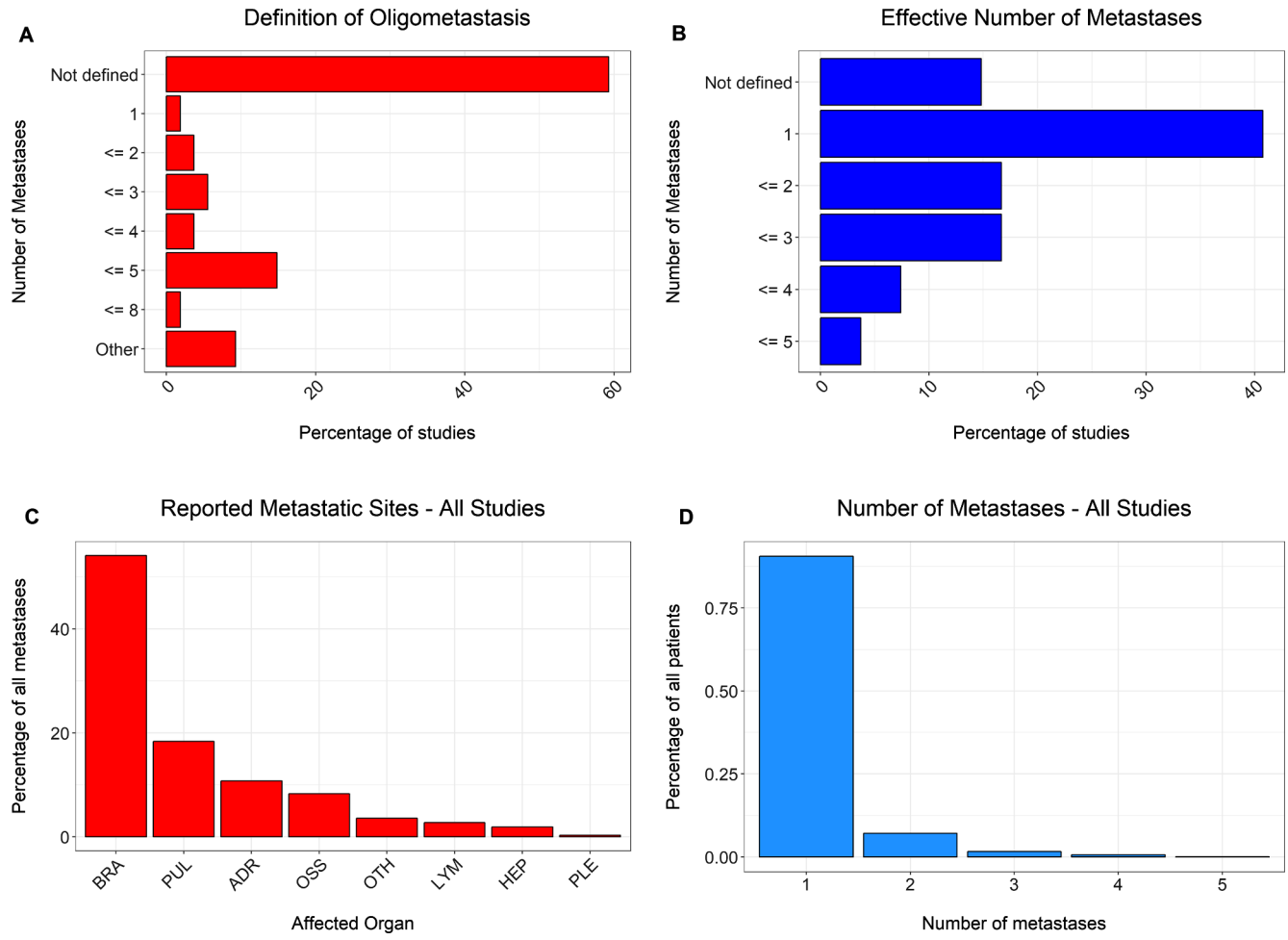


**Fig. 2.** (A) Definition of oligometastasis as described in included studies. (B) Effectively included maximum number of metastases per patient in studies. (C) Organ distribution of metastases as percentage of all metastases in all included studies. BRA – brain, PUL – lung, ADR – adrenal, OSS – bone, OTH – other, LYM – distant lymph nodes, HEP – liver, PLE – pleura. (D) Number of metastases per patient as percentage of patients in all included studies.

was coined in 1995. Radical treatment of metastatic patients was not firmly established in this period, leading to many studies that exclusively included patients with a singular metastasis. As there is no concise definition of the oligometastatic state today in terms of number or time interval of occurrence from first diagnosis, our analysis revealed widely varying numbers of treated metastases per patient with the majority of publications reporting fewer than three metastases (Fig. 2). On the other end of this spectrum is the study by Cheruvu et al. which defined up to eight metastases as "limited stage IV" [7]. Interestingly, a discrepancy between the prespecified number of lesions by a particular study and the actually treated and analyzed number of lesions could be detected. The vast majority of patients was characterized by a maximum of two metastases, although the respective study allowed a significantly higher number as a prespecified inclusion criterion (Fig. 2). For example, Merino et al. defined OMD as up to five metastases but only included two patients with two metastases, a single patient with three metastases and none with more than that, while 79% of patients actually only had a solitary metastasis [26]. Based on the publications included in this review, a definition of OMD based on the number of metastases would therefore have to be equal to or fewer than three metastases to reflect the published clinical practice. While an arbitrary number does most likely not reflect the underlying biology of OMD, its definition should be uniform in the absence of a better discriminator. Although the formal prespecified discrimination between synchronous and metachronous was either 3 or 6 months in those studies, these intervals between primary diagnosis and metastases defining metachronous disease were not reflected in the disease-free interval (DFI) of included patients: 14 studies reported actual median duration until diagnosis of metastases of 14.3 months, and 11 studies did not report a DFI.

Median OS of the analyzed studies was 19.6 months (6.2–52.9 months) with an observed plateau and possible long-term survival of 20%. No OS difference for synchronous and metachronous OMD could be detected in the present analysis in contrast to the individual patient-data meta-analysis from Ashworth et al. [1]. Of note, we observed a trend for improved median OS in the cited studies over time: patients from reports published after 2011 reported better OS compared to the earlier time period: 28.1 months versus 17.2 months, respectively. Whether this effect is related to a wider utilization of locally intensified treatment or improved treatment quality cannot be answered based on the available data. Rather, this effect coincided with more studies reporting on OMD as a distinct entity with a pre-specified, albeit not standardized definition of OMD.

Although there was no formal requirement on the imaging modality to define OMD in these studies, a lead time or stage migration bias cannot be excluded due to earlier, more stringent and improved imaging during staging and follow-up. Therefore, a better patient selection due to awareness of the OMD concept and staging with more vigorous imaging and follow-up after 2011 seems to be a more likely explanation for the increasing OS benefit over time, as patient with more widespread metastatic disease could then be excluded from intensified OMD treatment concepts. A similar stage migration and OS shift has been

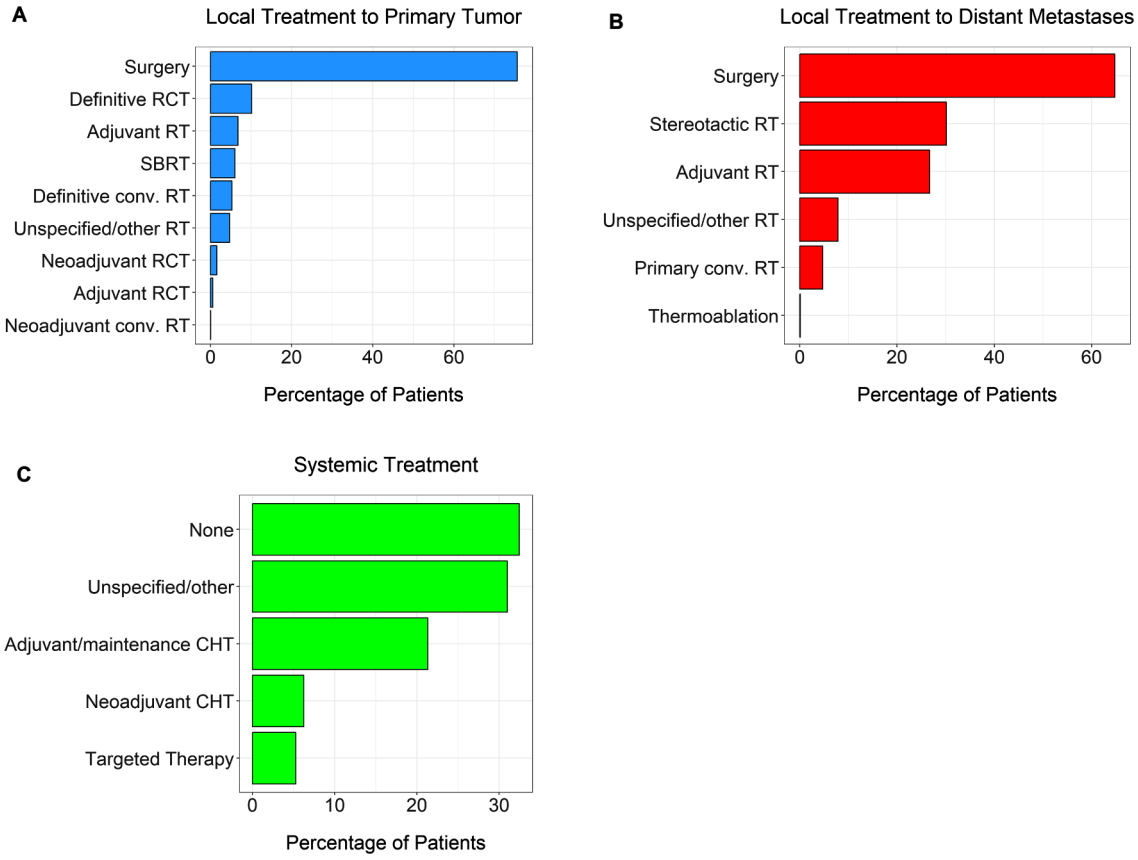


**Fig. 3.** Percentage of patients treated with indicated modality. (A) Local treatment to primary tumor. (B) Local treatment to distant metastases. C) Systemic treatment. RT – radiotherapy, SBRT – stereotactic body radiotherapy, RCT – radio-chemotherapy, CHT – chemotherapy.

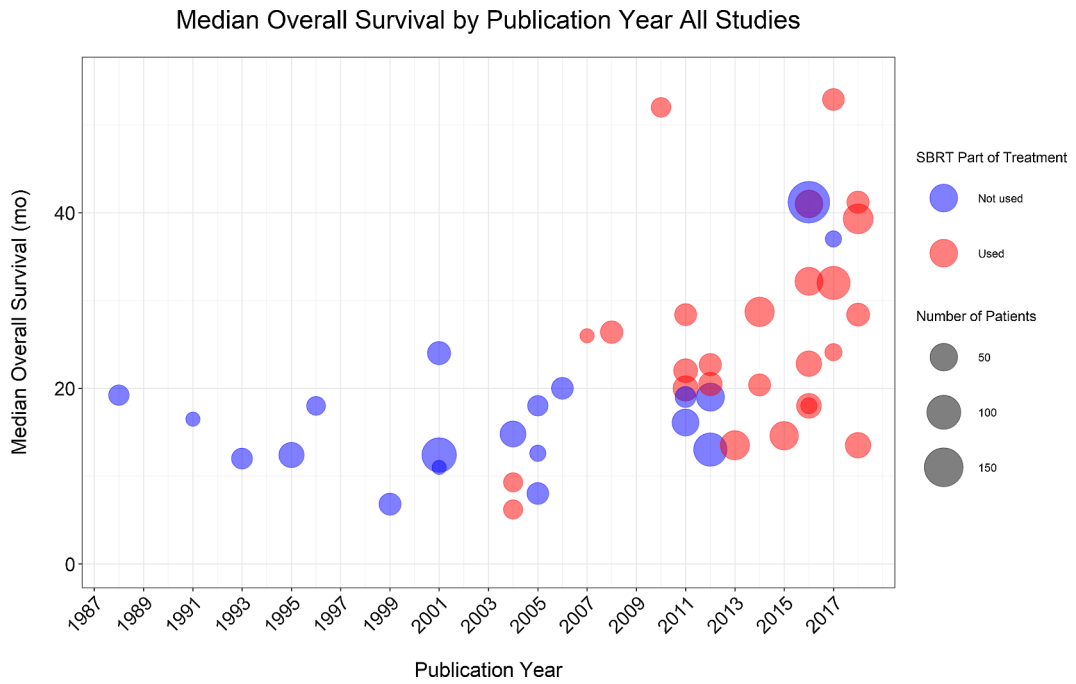


**Fig. 4.** Included studies by publication year (x-axis) and median overall survival of included patients (y-axis). Circle size is proportional to number of patients. Colors signify studies which reported use of SBRT as part of the locally ablative treatment regimen for primary tumor or metastases (red) or use of surgery only (blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observed with the vigorous implementation of PET-CT staging for non-metastasized NSCLC before radical treatment, as patients with distant metastases not detected by routine CT scans could be excluded from futile intensified curative treatment approaches [47].

The management of OMD has changed considerably over the past 20 years. Historically, chemotherapy has been the treatment of choice

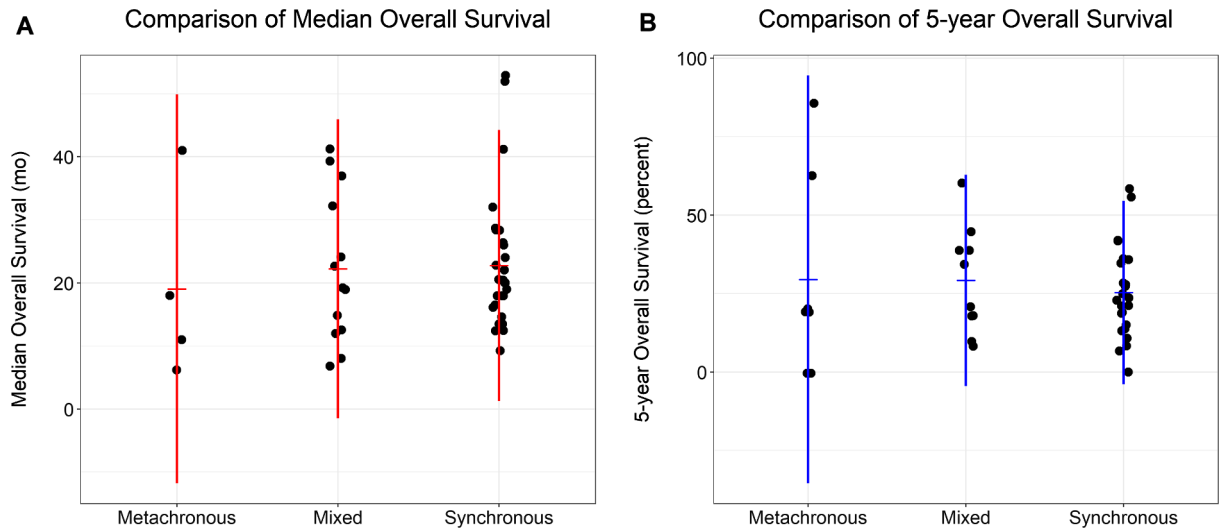


**Fig. 5.** Strip chart of (A) median OS and (B) 5-year OS, grouped by type of metastatic disease (synchronous, metachronous, mixed). Cross indicates mean, bars two standard deviations in each direction.

for metastatic disease with median OS times of well below 12 months [38,4,35]. This has changed significantly with the notion of OMD being a distinct entity, possibly benefiting from additional LAT and definitive treatment of the locoregional primary tumor and all oligometastases. When analyzing the patterns-of-care over time (Fig. 5), it can be perceived that initially the treatment of choice for metastases was surgery, while in studies published after 2011 radiotherapy, mostly in the form of SBRT, has almost surpassed surgical approaches. For the primary tumor, this development has not been as marked, as recommendations of primary treatment depends on the stage of intrathoracic disease.

When investigating the effects of the different LAT on OS and only comparing studies from the same time period (2011 onwards to avoid negative impact of inferior survival of older surgical series in the pre-SBRT era), no OS difference between surgery and radiotherapy, especially SBRT for distant metastases could be detected. This finding therefore supports the current clinical trend to increase the utilization of SBRT for ablative treatment of metastases and to incorporate it as a curative treatment option in clinical trial protocols. This may be explained by several factors. Firstly, it is known from non-metastatic disease that radiotherapy and surgery are equally effective in locally advanced NSCLC when added to chemotherapy [32,10]. In early stage NSCLC, SBRT has improved outcome compared to conventional radiotherapy [27,3] and available data indicate that differences to surgical lobectomy are at least small [6]. SBRT, when performed with sufficiently high doses and at experienced centers [36,16], also provides excellent outcome in OMD [23,41], which supports the finding of our study that the choice of surgery or radiotherapy does not affect survival. Secondly, despite the majority of patients traditionally receiving surgical resection, the available evidence was mostly retrospective; in contrast, radiotherapy has been the most frequently used local treatment modality in all modern prospective trials in oligometastatic NSCLC [8,19,13,14,28], of which two were able to achieve an OS

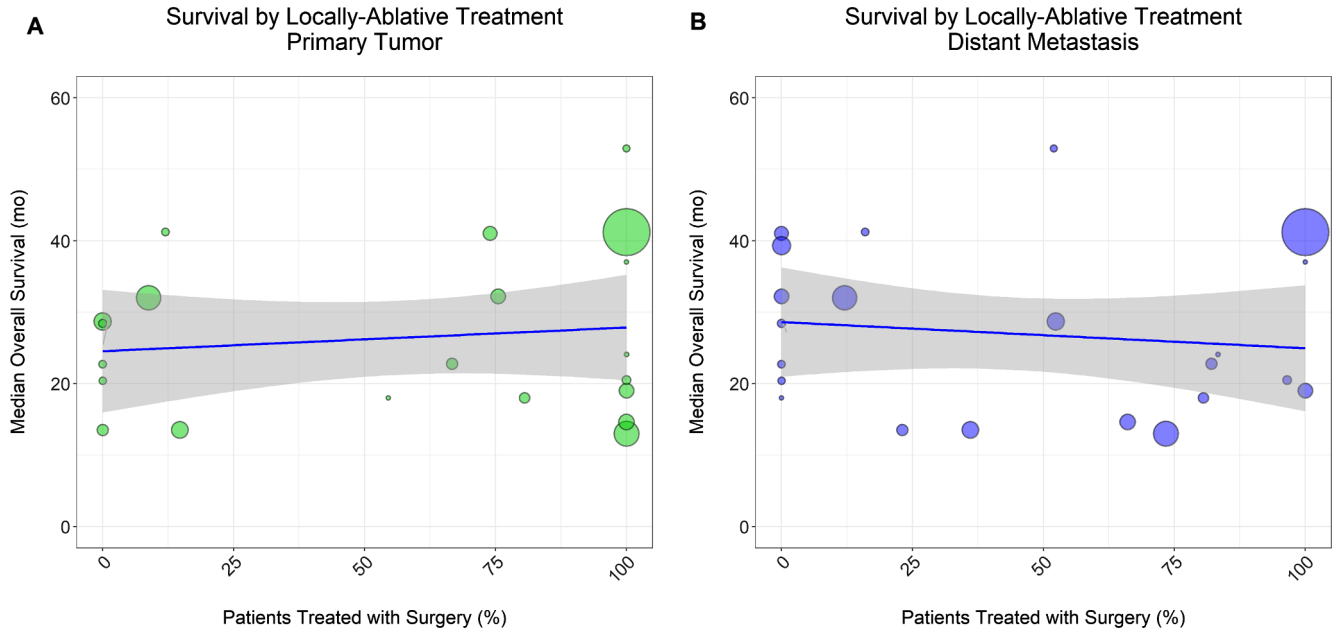


**Fig. 6.** Effect of locally-ablative treatment on median overall survival for all studies published after 2011. X-axis depicts percentage of patients treated with surgery as LAT in respective study for primary tumor (A) or distant metastases (B). Regression line (blue) is surrounded by 95%-confidence interval (grey). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

benefit making radiotherapy the local treatment modality with the highest level of evidence. Thirdly, radiotherapy has logistical advantages if oligometastases are located outside the lung and in particular, if several organs are involved: several separate and sequential surgical procedures would bear a risk of delaying systemic treatment, whereas radiotherapy usually allows simultaneous treatment at various sites and concurrent local and systemic treatment [21]. Fourthly, it is known that despite successful local treatment the majority of patients will develop distant disease progression without a curative potential. The choice of local treatment should therefore also consider the toxicity profile of the respective local treatment modalities and their influence on quality of life.

A time-trend in the use of systemic therapy has been observed as well: over time systemic therapy has been applied more frequently (eventually 75% of patients receiving systemic therapy) rendering it an integral part in the management of synchronous OMD. In synchronous patients, virtually all received systemic therapy as a backbone treatment compared to only 61% in metachronous OMD patients.

For synchronous oligometastases, multimodality treatment with integration of LAT may hence be advocated based on the available data. This is also supported by published literature showing a predominant pattern of local progression after systemic induction therapy, i.e. the primary tumor and initially detected metastases [9,44,45]. The pivotal question then is the ideal time point of LAT. As we are currently not able to reliably predict the course of disease after initial detection of OMD, a primary upfront LAT approach may represent an overtreatment. At this point in time, a proportion of patients may not represent a true OMD state but will eventually transform into poly-progression. Therefore, patient selection with induction systemic treatment has been advocated and implemented in the most recent prospective trials: Gomez et al. conducted a phase II randomized controlled trial to determine the progression-free survival (PFS) and OS benefit of LAT using surgery and/or radiotherapy for oligometastatic (up to three metastases) NSCLC patients. The study terminated early, because the group receiving radical treatment showed a much better PFS than the group treated with maintenance chemotherapy, only (11.9 months vs. 3.9 months) [13,14]. As shown at the ASTRO meeting 2018, this PFS also translated into an OS benefit (41.2 months vs. 17 months). Importantly, Gomez and colleagues included only patients that had $\leq 3$ metastases after an induction chemotherapy. Similarly, Iyengar et al. analyzed PFS in oligometastatic disease (up to five metastases) in a phase II study comparing ablative therapy plus maintenance chemotherapy to chemotherapy alone. Importantly, they also defined the oligometastatic state after induction chemotherapy. This study terminated early as well due to a marked PFS benefit in the radically treated group (9.7 months vs. 3.5 months) [19].

More recently, targeted therapy for oncogene-addicted tumors and immunotherapy have arisen as options that increase the life-span of some patients considerably and we are currently witnessing a paradigm shift in the treatment of stage IV NSCLC [12,40,46]. Still, the general principles and conclusions of this analysis apply, unless evidence emerges addressing these questions in an unequivocal way. Most interestingly, no studies included here reported on the use of immunotherapy for OMD, warranting further evaluation once data emerges.

The literature included in our analysis may be subject to several biases. A weakness is the loss of a sizable fraction of potential studies due to our definition of inclusion and exclusion criteria. However, we deemed this strategy necessary to reduce the enormous complexity introduced by varying study populations, treatment strategies and definition of metastatic states and radical treatment. The largely retrospective nature of studies without proper control cohorts and the remaining inhomogeneity in inclusion criteria makes drawing strong conclusions difficult. Moreover, a relevant uncertainty concerning the optimal management of OMD in NSCLC is the complete lack of published data on immunotherapy in this patient population. This is in strong contrast to its anticipated relevance in the future. Fortunately, published results of prospective trials are emerging and study activity recently increased within this patient population. Additionally, selection bias may be relevant, especially for retrospective studies, because radical treatment may have been offered preferentially to patients with a presumably better prognosis. With the majority of included publications being retrospective and not registered before analysis, publication bias may also play a role.

## Conclusions

While evidence is emerging that a radical treatment of OMD patients may yield an extended OS, most studies are still retrospective in nature and mainly evaluate patients with singular metastases. Moreover, the available literature is biased with respect to definition of oligometastatic disease (number and location of metastases, heterogeneous treatment regimens). Still, relevant time trends could be detected indicating a shift in treatment modalities for metastases-directed treatments (increasing use of SBRT) and an OS benefit over time mostly reflecting better imaging and staging and therefore better patient selection. Also, over time, studies tried to better pre-specify criteria for OMD, although no formal convergence of definitions could be detected.

Future efforts to improve data quality and the conclusions to be drawn from OMD studies should focus on (a) a formal separation and description of the different clinical scenarios of OMD, (b) formal criteria that define OMD (e.g. based on number of metastases or a definition of “low tumor burden“), and (c) implementing standardized imaging for detection and definition of OMD.

## Declaration of Competing Interest

Matthias Guckenberger, Daniel Schanne and Jana Heitmann certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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DHS and JH performed data acquisition and analysis. The manuscript was prepared by DHS, JH, MG and NA.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2019.101892.

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